Atherosclerosis and AD

Analysis of data from the US National Alzheimer's Coordinating Center

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Abstract—*Background:* Epidemiologic studies have implicated cerebrovascular disease and its antecedents as risk factors for Alzheimer disease (AD). Cerebral atherosclerosis or strokes may increase the deposition of neuritic plaques or the formation of neurofibrillary tangles. Alternatively, they may simply hasten the age at onset of disease, or increase the severity of disease symptoms. This investigation examined the association between cerebrovascular disease and the pathologic manifestations of AD in an autopsy series. *Methods:* This was a cross-sectional study using data from the United States National Alzheimer's Coordinating Center database. The primary analysis included 1,054 individuals with clinical information and semiquantitative neuropathologic measurements: 921 had AD as the primary neuropathologic diagnosis and 133 were considered neuropathologically normal. *Results:* Overall, 9% of the individuals had clinical history of stroke during life, but 33% had evidence of cerebral infarcts at postmortem. There was no association between neuritic plaques or neurofibrillary tangles, the primary neuropathologic manifestations of AD, with either clinical history of stroke or the presence of cerebral infarcts at postmortem. The authors did find a higher frequency of neuritic plaques and neurofibrillary tangles with increased amyloid angiopathy. Neither plaques nor tangles were associated with small vessel cerebrovascular disease, arteriosclerosis. However, the presence of large-vessel cerebrovascular disease, or atherosclerosis, was strongly associated with an increased frequency of neuritic plaques. *Conclusions:* Atherosclerotic cerebrovascular disease may have a role in the pathogenesis of Alzheimer disease, because of a strong association with frequent neuritic plaques.

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Epidemiologic studies have repeatedly suggested an association between cardiovascular risk factors, cerebrovascular disease, and the subsequent development of Alzheimer disease (AD).[1-5] While it is unusual for cerebrovascular disease to alone be the cause of progressive dementia,[6] both cerebrovascular disease and AD are frequent conditions during senescence, and often coexist.[1,7] Previous studies[8-12] have identified microvascular change or infarcts in the brains of patients with AD, but without linking the vascular lesions to the specific pathologic manifestations of AD.

Hypotheses explaining the association between cerebrovascular disease and AD include both direct and indirect effects. Blood vessel or brain parenchymal injuries may increase β-amyloid deposition or disrupt the blood–brain barrier, leading to oxidative stress or cytokine-mediated inflammation.[13-15] Alternatively, cerebrovascular disease might simply increase the severity of dementia or hasten the age at onset.[5,16-19] Cerebrovascular disease and AD share putative risk factors, such as apolipoprotein E (*APOE*) genotype,[20] plasma homocysteine levels,[21] or inflammatory cytokines.[22] *APOE*-ϵ4 allele could independently increase the risk of both disorders, without a direct causal link between the two,[23,24] but there is no consistent evidence of *APOE*-ϵ4-related risk in cerebrovascular disease.[25-27]

We used the United States National Alzheimer's Coordinating Center (NACC) database to investigate whether cerebrovascular disease by history, or by pathologic examination, contributed to the pathologic manifestations of AD, namely neuritic plaques and neurofibrillary tangles.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the February 8 issue to find the title link for this article.

Methods. *Dataset.* The NACC database (2002 dataset) as of February 2003 consisted of demographic and clinical data on 59,383 patients with dementia and controls, enrolled at 32 AD Centers in the United States funded through the National Insti-

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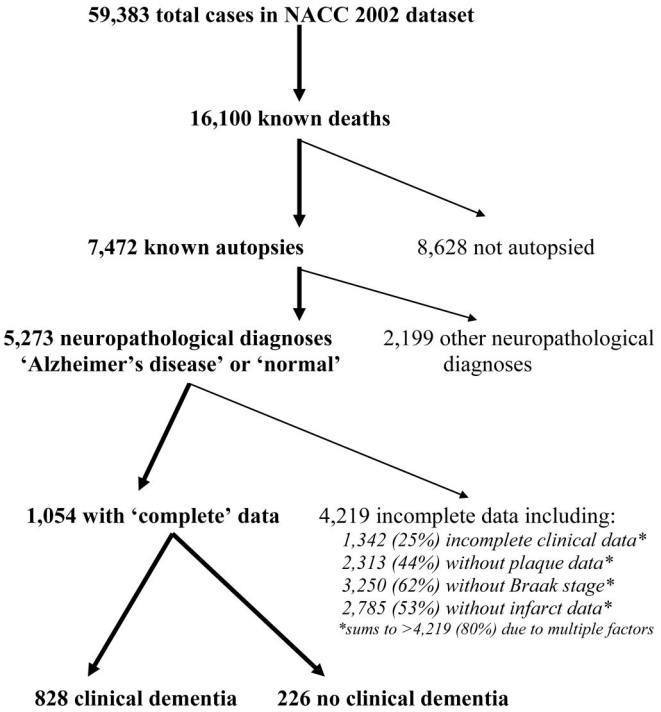

Figure. Diagram showing the selection of data that were usable for this study, extracted from the full National Alzheimer's Coordinating Center (NACC) dataset.

tute on Aging. These subjects are a referral population. The data were stored without personal identifiers. Each center has obtained Institutional Review Board approval. The Centers program began in 1985 and data were accumulated at each center from that time onwards, including demographic, clinical, and neuropathologic variables, though this process was not standardized across centers. NACC was established 14 years later in 1999, at which time data specified by NACC that were collected between 1985 and 1999 were entered into the NACC database. Between 1999 and 2002, subsequently acquired data specified by NACC were directly entered into the database.

Between 1985 and 2003, there were 7,472 autopsies performed among 16,100 known deaths (figure). To examine the association between cerebrovascular disease and AD, our primary analyses were restricted to cases with complete information regarding clinical diagnosis, stroke history, semiquantitative neuritic plaque counts,[28] and assessment of tangles by Braak staging.[29] This reduced the available data to a total of 1,054 autopsies, including 133 individuals considered pathologically normal and 921 individuals with the pathologic diagnosis of AD, using the criteria of the Consortium to Establish a Registry for AD (CERAD).[28] Among those with AD, 676 (73%) met criteria for definite, 88 (9.5%) probable, and 56 (6.1%) possible AD, and 101 (10.9%) had AD with concomitant Lewy body dementia. Data from other patients with AD were excluded because they lacked data for neuritic plaques, Braak stage, or infarcts (see the figure). Braak staging, introduced after publication in 1991,[29] was assessed on older cases by only a few centers, and was available in only 38% of cases (14% of those from 1985 to 1993 vs 41% of those from 1994 to 2003). Because some centers did not evaluate or report certain variables, leading to case exclusion, the dataset included information from autopsies performed between 1987 and 2002, at 22 of the 32 centers. The average interval between last evaluation and autopsy was 1.4 ± 1.8 (SD) years (83% were ≤2 years, 93% ≤4 years, 98% ≤6 years). At last clinical examination, 828 patients (79%) were demented, while 226 (21%) were not. Pathologic diagnoses did not always agree with the clinical diagnoses during life: 921 (87%) of the brains met neuropathologic criteria for AD, while only 133 (13%) were deemed pathologically normal. Thus in this set of 1,054 cases, a somewhat higher proportion of individuals met pathologic criteria than met clinical criteria for AD.

The characteristics of those included in the analyses were similar to those of the larger group of 5,273 autopsied individuals with normal or AD pathology (see the figure). Those included did not differ significantly from those excluded, in age (79.7 years vs 79.6 years), education (13.9 years vs 13.2 years), sex (52.8% vs 56.4% female), or race-ethnicity. The proportion of individuals with dementia (77.0% vs 80.4%), with a history of stroke (8.7% vs 11.8%), or with *APOE*-ϵ4 alleles (58.0% vs 57.8%) was also similar. To confirm the generalizability of our results, we also performed analyses using all relevant data from the NACC database, using for each analysis all subjects with relevant data for the particular question, without the above-described exclusion of cases with nonpertinent "incomplete" data.

Clinical variables included sex, race-ethnicity, age at onset of dementia, age at death, *APOE* genotype, history of stroke, and clinical diagnosis of dementia or no dementia. AD was diagnosed by National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria. Neuropathologic disease variables included primary neuropathologic diagnosis, and semiquantitative neuritic plaque counts as recommended by Consortium to Establish a Registry for Alzheimer's Disease.[28] Braak stages were classified as 0 for no tangles, and as I to VI according to the published criteria.[29] For most analyses these categories were collapsed, such that lesser stages 0 through IV were compared to higher stages V and VI, representing extensive neocortical neurofibrillary tangles. Neuritic plaques were rated as none, sparse, moderate, or frequent. Similarly, atherosclerosis was rated as none, mild, moderate, or severe. Infarcts were scored by type and rated only as present or absent in categories including parenchymal lesions due to large artery or lacunar (small artery) infarction, cortical microinfarction, and hemorrhage. We grouped large artery infarcts, lacunes, and microinfarcts as cerebral infarcts. Arterial pathology was rated, as per the NACC Neuropathology manual version 1.0 (available at https://www.alz.washington.edu/NONMEMBER/PDF/npded2004.pdf), with separate semiquantitative ratings (none, mild, moderate, or severe) for atherosclerotic disease of the large cerebral vessels of the circle of Willis, arteriosclerotic disease of the small parenchymal arterioles, and microscopic amyloid angiopathy. The macroscopically visible atherosclerosis of large vessels was rated during gross examination of the circle of Willis at the base of the brain. Microscopically evident arteriosclerotic occlusive disease and amyloid angiopathy of small parenchymal vessels was rated during microscopic evaluation of stained paraffin brain sections. Neuropathologic assessments were independently rated at each site, in compliance with the NACC Neuropathology manual, but without standardization across the participating sites.

Data analysis. The initial analyses examined the association between frequent neuritic plaques or extensive neocortical neurofibrillary tangle stages (Braak V/VI) and variables indicating cerebrovascular disease. These included history of a clinical stroke, pathologically assessed strokes (including large artery infarcts, lacunes, or microinfarcts), amyloid angiopathy, arteriosclerosis, and atherosclerosis. Further analyses were then performed, stratifying by the presence or absence of dementia during life, to examine any differential effect of cerebrovascular disease on clinical diagnosis. In some analyses of atherosclerosis, we stratified by the presence of neuropathologically identified infarcts.

For categorical variables, χ^2 was used, and for continuous variables we used either analysis of variance or Student's *t*-test. Our principal analyses included univariate and multivariate logistic regression with Braak stage and plaque counts as outcomes. Predictors included stroke, infarct, atherosclerosis, arteriosclerosis, and amyloid angiopathy. Covariates included age, sex, and *APOE* genotype. In these models we calculated an OR with 95% CI. We used SPSS for Windows version 11.0.1 for analyses. Based on examination of the unadjusted data, logistic regression models were constructed to examine the risk of having frequent neuritic plaques by the four levels of atherosclerosis using all other categories of neuritic plaques (none, sparse, and moderate combined) as the reference group. Unadjusted ORs were calculated first, followed by models adjusted for age, sex, and relevant covariates. Subsequent models were stratified by the presence or absence of dementia during life, or by the presence or absence of infarcts identified at postmortem examination, or by *APOE* genotype. In order to assess the potential impact of intercenter variability we conducted two additional regression analyses using SAS for Win-

Table 1 *Demographic and clinical information*

	Demented	Not demented
No. of autopsy cases	828	226
% Female	51.8	56.6
% White	97.2	100.0
Education, y, mean (SD; n)	13.5 (3.5; 780)	15.3 (3.1; 219)
Stroke by history, %	10.3	3.1
Neuropathologic stroke, %	30.4	40.3
Age at death, y, mean (SD)	78.8 (8.8)	82.9 (10.0)
Age at onset of dementia, y, mean (SD)	68.9 (9.2)	Not applicable
APOE ε4 allele present, n (%)	382 (67.0)	140 (35.7)

n = Number of cases (not all cases had information on education and *APOE* genotype).

dows version R8.2. In the first of these models, generalized estimating equations (GEE) were used in which each center was treated as a cluster assuming that there was less variation within than across the centers.[30,31] For the second model, conditional logistic regression models were conducted, in which each center was considered as a separate stratum, and with subsequent summation across strata.[32]

Results. Overall, unadjusted comparisons revealed that individuals with dementia were significantly younger than those without dementia and had less education (table 1), but did not significantly differ in sex (51.8% vs 56.6% women; see table 1). A history of stroke was reported in 8.7% of individuals, and was more frequent among those with dementia than those without (10.3% vs 3.1%; $\chi^2 = 11.5$, $df = 1$, $p = 0.001$). In contrast, neuropathologic evidence of stroke (large, lacunar, or microscopic infarct) was present in 32.5% of cases, but was somewhat less frequent in those with dementia than in those without dementia (30.4% vs 40.3%; $\chi^2 = 7.8$, $df = 1$, $p = 0.005$).

Univariate analyses. Neuritic plaques and cerebrovascular disease. Adjusting for age and sex, there was no significant association between the number of neuritic plaques and either clinical stroke or neuropathologic infarcts (table 2). This was true for large infarcts, lacunes, and microinfarcts combined, and also true when each infarct type was examined separately (data not shown). Neuritic plaques were strongly associated with amyloid angiopathy (see table E-1 on the *Neurology* Web site at www.neurology.org), and with the presence of cerebrovascular arterial disease, regardless of clinical diagnosis. This association was due to large-vessel atherosclerosis (table 3), rather than small-vessel arteriosclerosis. As noted in table 3, individuals with atherosclerosis were more likely to have the highest frequency of plaque counts. A relationship between severity of atherosclerosis and frequency of neuritic plaques was also evident (table 4). Moreover, this association persisted regardless of the presence or absence of cerebral infarcts identified at postmortem examination (see table E-2 on the *Neurology* Web site at www.neurology.org).

Table 2 *Relation of clinical stroke and neuropathologic infarcts to neuritic plaque counts and to Braak stage*

	Demented		Not demented	
Neuritic plaques	Stroke	No stroke	Stroke	No stroke
None/sparse	8 (9.4)	71 (9.6)	3 (42.9)	73 (33.3)
Moderate	12 (14.1)	111 (14.9)	0	31 (14.2)
Frequent	65 (76.5)	561 (75.5)	4 (57.1)	115 (52.5)
	Any infarct	None	Any infarct	None
None/sparse	22 (8.7)	57 (9.9)	30 (33.0)	46 (34.1)
Moderate	35 (13.9)	88 (15.3)	12 (13.2)	19 (14.1)
Frequent	195 (77.4)	431 (74.8)	49 (53.8)	70 (51.9)
	Demented		Not demented	
Braak stage	Stroke	No stroke	Stroke	No stroke
0/I/II	5 (5.9)	41 (5.5)	4 (57.1)	95 (43.4)
III/IV	12 (14.1)	162 (21.8)	3 (42.9)	90 (41.1)
V/VI	68 (80.0)	540 (72.7)	0	34 (15.5)
	Any infarct	None	Any infarct	None
0/I/II	14 (5.6)	32 (5.6)	41 (45.1)	58 (43.0)
III/IV	42 (16.7)	132 (22.9)	36 (39.6)	57 (42.2)
V/VI	196 (77.8)	412 (71.5)	14 (15.4)	20 (14.8)

Values are n (%).
Table shows actual numbers of brains (without any adjustments) crosstabulated for stroke or "any infarct" (large, lacunar, or microinfarct) vs Alzheimer pathology, stratified for presence or absence of dementia. Chi-squared tests reveal no significant trends.

Table 3 *Relation of cerebral atherosclerosis to neuritic plaque counts and Braak stage*

	Demented		Not demented	
	Atherosclerosis present	No atherosclerosis	Atherosclerosis present	No atherosclerosis
Neuritic plaques	*		†	
None/sparse	18 (5.2)	53 (13.4)	45 (34.1)	22 (31.4)
Moderate	39 (11.3)	72 (18.2)	10 (7.6)	18 (25.7)
Frequent	287 (83.4)	271 (68.4)	77 (58.3)	30 (42.9)
Braak Stage			‡	
0/I/II	18 (5.2)	26 (6.6)	48 (36.4)	39 (55.7)
III/IV	71 (20.6)	93 (23.5)	70 (53.0)	17 (24.3)
V/VI	255 (74.1)	277 (69.9)	14 (10.6)	14 (20.0)

Values are n (%). The table shows the actual numbers of brains (without any adjustments) crosstabulated for atherosclerosis vs Alzheimer pathology, stratified for presence or absence of dementia. Total n = 942, for both plaque count and Braak stage analyses, because in 112 cases atherosclerosis information was not available.

* $\chi^2 = 24.0$, $df = 2$, $p < 0.0001$; † $\chi^2 = 13.0$, $df = 2$, $p = 0.001$; ‡ $\chi^2 = 15.7$, $df = 2$, $p = 0.0004$.

Braak stage and cerebrovascular disease. There was no significant association between Braak stage and either clinical stroke or neuropathologic infarct (see table 2). This was true for large infarcts, lacunes, and microinfarcts combined as a group, or when each infarct type was examined separately. The highest Braak stage was associated with increased frequency of amyloid angiopathy (see table E-1). There was an inconsistent, non-monotonic association between Braak stage and the presence of atherosclerosis in persons without dementia, only in the unadjusted analysis (see table 3), not seen in the multivariate analysis.

Multivariate analyses. Association of neuritic plaques or Braak stage with stroke. There was no association between neuritic plaques and stroke by history or neuropathologic examination, regardless of the presence of dementia during life. Neurofibrillary tangles were weakly associated with stroke. The presence of extensive neurofibrillary tangles (Braak stage V/VI) was twice as likely (OR 2.0; 1.2 to 3.3, $p = 0.007$) to be associated with a history of stroke than the reference group composed of all of the lower Braak stages (Braak 0/I/II/III/IV). Among those with dementia, the association was weaker (OR 1.4; 0.8 to 2.5; $p > 0.05$), and in those without dementia, the OR could not be calculated due to absence of individuals in the higher Braak stage with stroke. Braak stage was not related to the presence of neuropathologic infarcts identified at postmortem examination, regardless of the presence or absence of dementia.

Association of neuritic plaques or Braak stage with cerebrovascular arterial pathology. Multivariate analyses, adjusting for age and sex, confirmed a highly significant association between neuritic plaques (frequent, compared with reference group consisting of those with none/sparse/mild/moderate plaques) and cerebrovascular arterial pathology (see table 4). The association increased in strength as the degree of atherosclerosis increased. In addition, the association between any degree of atherosclerosis and neuritic plaques was stronger in those with dementia (OR = 3.0; 2.1 to 4.3, $p < 0.0001$) than in those without a history of dementia (OR = 2.2, 1.1 to 4.4; $p = 0.02$). The association between neuritic plaques and arterial pathology was due to atherosclerosis, not arteriosclerosis. Atherosclerosis was greater among those with the highest frequency of neuritic plaques, and was independent of strokes. As noted in table 4, the association remained significant when adjusted for the presence or absence of brain infarcts. These analyses were repeated, stratified by the presence or absence of brain infarcts,

Table 4 *Association between cerebral atherosclerosis and neuritic plaques*

	Neuritic plaques					
Atherosclerosis	None to moderate	Frequent	Model 1, unadjusted	Model 2, adjusted for age, sex, and cerebral infarct	Model 3, adjusted for center (conditional)	Model 4, adjusted for center (random effects)
None	165 (35.4)	301 (64.6)	1.0 reference	1.0 reference	1.0 reference	1.0 reference
Mild	75 (30.0)	175 (70.0)	1.3; 0.9–1.8	1.6; 1.1–2.4*	1.6; 1.1–2.6†	1.6; 0.6–4.6
Moderate	26 (19.0)	111 (81.5)	2.3; 1.5–3.7‡	3.4; 2.0–5.6‡	3.3; 1.8–6.2§	3.3; 1.03–10.6‖
Severe	11 (12.4)	78 (87.6)	3.9; 2.0–7.5‡	5.8; 2.9–11.8‡	5.1; 2.4–11.1‡	5.7; 1.3–25.5¶

Values are n (%) or OR; 95% CI. Model 1 is the unadjusted logistic regression comparing the category of plaque frequency by the severity of atherosclerosis. Model 2 is the multivariate logistic regression adjusting for age, sex, and the presence or absence of cerebral infarcts at postmortem examination. Model 3 is a conditional logistic regression model in which each center is considered as a stratum and the effects are adjusted across strata. Model 4 is a logistic model using generalized estimating equations in which each center is treated as a cluster as in a random effects model; the effects are then adjusted across clusters.

* $p = 0.007$; † $p = 0.03$; ‡ $p < 0.0001$; § $p = 0.0002$; ‖ $p = 0.05$; ¶ $p = 0.05$.

with similar results (see table E-2). Braak stage was not related to arterial pathology of any type.

Effects of apolipoprotein E genotype. We performed additional multivariate analyses in a subsample (51%) of the cohort for which *APOE* genotypes were known, to determine whether *APOE*-ϵ4 might be responsible for the relationship between plaques and atherosclerosis, since *APOE* is related to serum cholesterol levels,[33,34] and atherosclerosis,[35,36] as well as a risk factor for AD. We did observe a strong association between the *APOE* ϵ4 allele and the presence of neuritic plaques ($\chi^2 = 47.7$, $df = 3$, $p < 0.0001$), but there was no relation between presence of atherosclerosis and *APOE* genotype. The association between neuritic plaques and atherosclerosis, adjusted for *APOE* ϵ4 allele, remained significant although the strength of the association was slightly decreased. Compared to those with no atherosclerosis, the risk of having increased plaques, adjusted for age, sex, and *APOE* genotype, remained increased for advanced stages of atherosclerosis (mild OR 1.0, 0.5 to 1.6; moderate OR 2.4, 1.2 to 4.8, $p = 0.02$; or severe OR 3.7, 1.6 to 8.7, $p = 0.003$, atherosclerosis).

Association of neuritic plaques and Braak stage with amyloid angiopathy. The presence of amyloid angiopathy was strongly related to the frequency of neuritic plaques (OR 3.1, 2.3 to 4.2, $p < 0.0001$). The association was also significant when stratified by dementia: it was present in those with dementia (OR 3.3, 2.2 to 4.8, $p < 0.0001$), and in those without dementia (OR 3.1, 1.7 to 5.0, $p = 0.0001$). Amyloid angiopathy related to Braak stage only for those with dementia (OR 1.9, 1.3 to 2.8, $p = 0.001$).

Intercenter variation. We performed additional analyses to assess whether the observed association between neuritic plaques and atherosclerosis might relate to intercenter variation in rating of atherosclerosis. Overall, there were 49%, 27%, 15%, and 9% subjects with no, mild, moderate, and severe atherosclerosis. However, the proportion with no atherosclerosis varied from 0% to 100% among the 22 centers with data. Excluding those six centers contributing fewer than 10 subjects each, the proportion still varied from 7% to 100% among the 16 remaining centers. A GEE analysis in which data from each center were clustered, similar to a random-effects model, was completed to adjust for variability across centers. However, the association between neuritic plaques and cerebrovascular atherosclerosis remained significant (see table 4). Subsequently, the main analysis was repeated using conditional logistic regression, conditioning on each center. Once again the association between neuritic plaques and atherosclerosis was unchanged (see table 4).

Generalizability of results. To assess whether the results might relate to exclusion of cases with incomplete data, the same multivariate logistic regressions as in table 3 and table E-2 were performed in the largest possible sets, stratified and unstratified, for all cases with pertinent information. Neuritic plaques remained strongly associated with atherosclerosis among 2,061 individuals with plaque counts (1,371 demented, 690 not demented; see tables E-3 and E-4). Lack of association between Braak stage and atherosclerosis persisted in the 1,607 (989 demented, 618 not demented) individuals with Braak information (see tables E-3 and E-4).

Discussion. Stroke was a frequent neuropathologic finding among persons with and without dementia; large, lacunar, or microscopic infarcts were evident in 34% of the autopsy series. A history of stroke was more frequent among patients with dementia than among persons without dementia. However, neuropathologic evidence of stroke was not different for those with and without dementia. Notably, the majority (79.6%) of individuals with neuropathologic evidence of stroke did not have a history of stroke during life. These strokes either represent infarcts occurring late, perhaps as a terminal event in the clinical course or earlier as "silent" cerebrovascular ischemic events. Silent infarcts, recognized by brain imaging in otherwise healthy elderly individuals,[4,5] appear to relate to the same vascular risk factors as clinically overt strokes.[4,5]

Neither a history of stroke nor neuropathologic evidence of cerebral infarcts at postmortem examination was associated with the main pathologic manifestations of AD, neuritic plaques or neurofibrillary tangles. Adjusting for age at death, there was no evidence for an effect of stroke on the frequency of neuritic plaques or neurofibrillary tangles in the brain, as might be expected if strokes, or silent brain infarcts, influenced the development of AD. Thus, an interpretation of these observations is that contributions of frank infarcts from cerebrovascular disease might be independent from the effects of plaques and tangles on clinical manifestations of dementia in AD; however, other contributions of cerebrovascular atherosclerotic disease might contribute to the actual pathology of AD.

Cerebrovascular arterial pathology did relate to one of the major pathologic manifestations of AD, neuritic plaques, but not to neurofibrillary tangles. This association was due to large-vessel atherosclerotic disease, not to small-vessel arteriosclerosis. (Amyloid angiopathy was associated with both neuritic plaques and neurofibrillary tangles, but this was expected because it is well established that the presence of β-amyloid in cerebral blood vessels occurs frequently in the elderly and accompanies AD.[37,38]) In at least one transgenic mouse model of AD, a similar relationship between atherosclerosis and β-amyloid deposits has been demonstrated.[49] The link between atherosclerosis and AD pathology is also not inconsistent with epidemiologic studies that have observed a relation between systemic atherosclerosis and clinically diagnosed AD.[1,39,40] But two earlier pathologic studies, including 38 patients from Finland[41] and 147 patients from Japan,[42] did not find the association between cerebral atherosclerosis and neuritic plaques observed here. Differences between their results and ours may relate to the methods of semiquantitative neuropathologic examination, but more likely owe to different selection criteria for brains. For the Finnish study,[41] the patient population "excluded all case subjects in whom cerebrovascular disease might be a significant contributor to dementia." In the Japanese study,[42] cases were

selected from a geriatric hospital, and only the infracerebral carotid and basilar arteries were examined. Other factors such as smaller sample sizes or differing race-ethnicity may also explain the differences in the results of these studies.

We found no evidence of any systematic bias in the rating of atherosclerosis with respect to neuritic plaques. Although there was no standardization across the centers, standard neuropathologic criteria were used at each center. Moreover, atherosclerosis was rated upon inspection of the circle of Willis, at the time of dissection of the gross brain, some days or weeks prior to the microscopic examination required for assessment of extent of plaques and tangles, and the ultimate neuropathologic diagnosis. Semiquantitative measurement of atherosclerosis did relate to the presence of brain infarcts, as might be expected: for patients without infarcts 63%, 22%, 10%, and 5% of cases had none, mild, moderate, and severe atherosclerosis, while for those with infarcts the distribution was 17%, 35%, 25%, and 21%. Any difference in the frequency of atherosclerosis across centers most likely reflects the regional or center-specific methods of recruitment of patients and controls at these sites. In this dataset derived from multiple centers, our two secondary analyses show that center-specific selection bias was also unlikely to be an explanation for our results. Furthermore, the observed association persisted, showing the stability of the findings, when more than double the number of individuals was included by relaxing requirements for data completeness. Classification bias is also unlikely, because if atherosclerosis was misclassified, it was non-differential to the presence of neuritic plaques, and such misclassification would favor the null hypothesis of no association.

Atherosclerosis can be associated with neuritic plaque frequency in several ways. Atherosclerosis leads to cerebral infarcts, which in turn could influence the deposition of β-amyloid in the form of plaques. However, the data here show a lack of significant association of presence vs absence of either clinical strokes or neuropathologic infarcts with severity of plaque or tangle pathology; this makes infarcts an unlikely reason for the association, although it is possible that the assessment of infarcts was insufficiently detailed to reveal such a relationship. Alternatively, atherosclerosis and β-amyloid containing neuritic plaque pathology may each independently relate to some common genetic or systemic factors, which have not as yet been identified. Finally, atherosclerosis itself might be influencing the parenchymal deposition of β-amyloid. One genetic factor could be the *APOE* genotype.[35,36] However, the association between atherosclerosis and neuritic plaques that we observed remains significant even after adjustment for the presence or absence of ϵ4 alleles, for which we have data for half the population. Despite the missing data, this suggests an effect of atherosclerosis independent of that of *APOE*. Other genetic factors, homocysteine levels,[21] cholesterol metabolism,[43] or diabetes[44] might be contributing factors, as each of these have been implicated in the processing of β-amyloid, the major constituent peptide in the neuritic plaque. Interestingly, recent epidemiologic studies[44-46] suggest that these risk factors in the elderly may be most potent when present in combination. Combination of cerebrovascular risk factors would also predispose to atherosclerosis. Atherosclerotic cerebrovascular pathology might itself directly influence amyloid deposition and the development of AD through a variety of mechanisms, relating to subclinical ischemia, distal atheromicroembolization, increased parenchymal oxidative stress,[15] or blood pressure dysregulation, which might affect blood-brain barrier integrity[47] influencing local production of β-amyloid, deposition of β-amyloid from the systemic circulation,[48] or its parenchymal clearance.

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